Mini Review

Interventional Cardiology

Mitigating cardiovascular risk from the isosorbide dinitrate-sildenafil interaction: A quality by design -optimized analytical method for therapeutic drug monitoring strategy

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Abstract

Public health, particularly for the elderly population, continues to be our foremost concern, with ongoing monitoring to ensure well-being. This emphasis stems from the understanding that functional health in advanced age arises from the accumulated impacts of diseases and natural physiological alterations associated with aging notably. Angina pectoris predominantly affects individuals aged 60 and above, highlighting the vulnerability of this demographic in terms of treatment options. Isosorbide dinitrate is an FDA-approved medication indicated for the prevention of angina pectoris caused by coronary artery disease. However, patients should be aware that this drug lacks the rapid onset required to halt an angina attack that is already underway, necessitating alternative interventions for acute episodes. By prioritizing preventive strategies and education, we aim to enhance quality of life and reduce health risks in older adults.

Keywords: Public health; Cardiovascular risk; Therapeutic drug; Coronary artery disease

Introduction

In 2006, sildenafil and tadalafil ranked as the 32nd and 74th most commonly dispensed prescription medications in the United States, respectively [1]. Erectile Dysfunction (ED) now impacts over 30 million men in the US and more than 150 million globally, with projections indicating further rises due to aging demographics. Phosphodiesterase-5 (PDE5) inhibitors (PDE5Is)-including sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis)-remain the primary first-line treatment for ED, effectively addressing symptoms by promoting vascular relaxation. Demand for PDE5Is is on the upswing, driven in part by their role as frontline therapies for Pulmonary Arterial Hypertension (PAH), where sildenafil (revatio) and tadalafil (adcirca) are commonly prescribed to improve pulmonary blood flow and patient outcomes. This dual application underscores their broadening therapeutic value in modern medicine [1-4]. These must never be taken by patients using nitrate preparations like Isosorbide dinitrate. The combination can cause a severe and dangerous drop in blood pressure, leading to collapse, unconsciousness, and could be fatal. Furthermore, patients must not stop taking their Isosorbide dinitrate in order to take one of these erectile dysfunction medications, as this would increase the risk of an angina attack. This safety information is consistent with the official prescribing documents (SmPC) and Patient Leaflets (PIL) approved by regulatory authorities like the Food and Drug Administration (FDA) and Medicines and Healthcare products Regulatory Agency (MHRA) [5]. The primary aim of this research is to develop and validate a novel,

robust, and environmentally friendly analytical method for the simultaneous quantification of isosorbide dinitrate) and sildenafil in human plasma, with the goal of addressing the severe drug interaction risks between these medications, especially in elderly patients, and supporting Therapeutic Drug Monitoring (TDM) and clinical safety screening [6].

Literature Review

Isosorbide dinitrate belongs to the group of medicines called nitrates. It works by relaxing the blood vessels and increasing the supply of blood and oxygen to the heart while reducing its work load. When used regularly on a long-term basis, this helps prevent angina attacks from occurring [7,8]. Sildenafil serves as the pioneering oral medication for erectile dysfunction. It is also a safe and effective oral treatment for male erectile dysfunction without known organic causes, and it could signify a new category of peripherally acting drugs for addressing this condition [9]. The pharmacological action of this medication is mediated by its ability to potently and selectively inhibit the catalytic site of Phosphodiesterase Type 5 (PDE5), an enzyme that hydrolyses cyclic Guanosine Monophosphate (cGMP). PDE5 is abundant in vascular smooth muscles, including those of penile arteries and corpora cavernous [10]. It is contra-indicated in patients who may require organic nitrates, such as ISDN, because this combination may cause a sudden drop in blood pressure by inhibiting the phosphodiesterase type 5 enzyme [11]. Additionally, sildenafil is effective in treating cardiovascular disorders secondary to endothelial dysfunctions [12-14].

Therapeutic Drug Monitoring (TDM) (involves the medical approach of testing certain medications at set times to ensure steady levels in a patient's blood, which helps tailor personalized dosing plans [15]. For most drugs, TDM is not needed for the vast majority of drugs and is chiefly utilized for those with narrow therapeutic indices, substantial variability in pharmacokinetics, therapies where target levels are challenging to assess, and agents capable of producing both therapeutic and adverse reactions. This process of quantifying drug levels to inform prescribing decisions is vitally essential when combining Isosorbide Dinitrate (ISDN) with sildenafil. As a phosphodiesterase-5 inhibitor, sildenafil strongly enhances the vasodilating actions of nitrates such as ISDN, which could result in profound hypotension, fainting, heart attack, or cardiovascular failure [16,17].

To mitigate this risk, this mentioned article introduced a novel analytical method that has been developed and validated a for the simultaneous TDM of these drugs in biological fluids to be applicable in clinical laboratories, can also be utilized in the routine Quality control laboratories in pharmaceutical companies and research centers to detect both Active Pharmaceutical Ingredients (APIs) in combination matrix and as individual drugs. This method enables clinicians to accurately detect both compounds, aiding in predicting patient risk and preventing adverse events [18-20].

Discussion

Furthermore, the method was designed with sustainability in mind, adhering to green chemistry principles. Sustainability is often used interchangeably with greenness. Green Analytical Chemistry (GAC) provides a framework for developing environmentally sustainable pharmaceutical analysis. Its core mission is to minimize ecological impact and improve operator safety without compromising analytical effectiveness. Guided by 12 key principles, GAC helps quality control analysts achieve this by reducing hazardous reagents, conserving energy, and minimizing waste. This approach is essential for creating eco-friendly routine testing protocols in the pharmaceutical industry.

This study employed a Quality-by-Design (QbD) framework for method development, utilizing a two-level full factorial design to systematically optimize experimental conditions, ensuring both robustness and environmental friendliness. QbD is one of the fundamental criteria in addition to safety and efficacy for any entity to be qualified and approved as a drug. For ensuring consistency of performance of pharmaceutical products and systems, the recent emphasis has been on building the "quality" rather than merely testing it. This philosophy forms the basis of Quality by Design (QbD). ICH guidance Q8 (R2) describes QbD as, "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

This method is applicable for Determination of ISDN and Sildenafil in their pharmaceutical preparations. The proposed method was used to quantify the studied drugs in their pharmaceutical formulations individually (Isordil® 40 mg tablets and Viagra® 50 mg tablets) without interference from common excipients, so this method can be used on Quality control laboratories

The primary objective of this research was to develop and validate a novel, robust, and environmentally friendly analytical method capable of the simultaneous quantification of Isosorbide Dinitrate (ISDN) and Sildenafil (SIL) in human plasma. This endeavor was motivated by a critical public health need: to mitigate the severe, potentially fatal drug interaction between these two commonly prescribed medications, particularly in the vulnerable elderly population. The successful application of this method to spiked human plasma, calibrated specifically within their therapeutic windows, confirms its direct relevance and utility for Therapeutic Drug Monitoring (TDM) and clinical safety screening.

The pharmacokinetic profiles of ISDN and SIL present a significant analytical challenge due to their differing concentration ranges in

the bloodstream. ISDN, used for angina prophylaxis, is almost fully absorbed after oral administration but suffers from extensive and highly variable first-pass hepatic metabolism, leading to a bioavailability range of 10% to 90%. This variability underscores the necessity for monitoring its plasma levels. Literature reports indicate that after a 10 mg oral dose, the mean peak plasma concentration (Cmax) of ISDN is approximately 21.4 ± 8.2 ng/mL, with a range of 11.0 to 33.9 ng/mL. For a higher, yet common, 40 mg dose, the plasma concentration would be proportionally greater. In stark contrast, sildenafil, used for erectile dysfunction, achieves significantly higher plasma concentrations. It's reported Cmax ranges from 127 ng/mL for a 25 mg dose to 1150 ng/mL for a 200 mg dose. This substantial disparity in expected plasma levels-with SIL often being an order of magnitude higher than ISDN required a method with a wide dynamic range and specific sensitivity for the lower-concentration analyte, ISDN.

The developed method successfully met this challenge. It demonstrated a sensitivity down to 50.0 ng/mL for ISDN and 25.0 ng/mL for sildenafil. This limit of quantification is particularly crucial for ISDN, as it is adequately low to detect the drug at concentrations relevant to its therapeutic use following standard doses, ensuring the method's applicability in real-world clinical scenarios. By implementing this optimized procedure, the analysis of spiked plasma samples yielded strong linear relationships over the calibrated range. The high correlation coefficients of the corresponding regression equations confirm the method's excellent performance and reliability for accurate quantification across the expected concentration spectrum of both drugs.

Furthermore, the method exhibited high selectivity, successfully distinguishing the two analytes from potential interferents present in the complex biological matrix of human plasma. This selectivity is a cornerstone of the method's validity, ensuring that the measured concentrations are unequivocally attributable to ISDN and SIL alone. The achievement of satisfactory recovery percentages further validates the efficiency of the sample preparation process, confirming that the analytes are effectively extracted from the plasma matrix without significant loss or degradation.

Conclusion

In summary, this study successfully bridges a critical gap in clinical pharmacology and patient safety. The developed method is not only grounded in the sound scientific principles of Quality-by-Design and Green Analytical Chemistry but is also rigorously validated for its intended purpose. Its ability to simultaneously, selectively, and sensitively quantify ISDN and sildenafil in a biological matrix directly addresses the dangerous interaction between these drugs. By providing a practical tool for TDM, this method empowers clinicians and researchers to monitor compliance, assess patient risk, and prevent catastrophic hypotensive events. This work ultimately contributes to a safer therapeutic landscape for the growing population of patients who may be exposed to this high-risk drug combination, aligning analytical science with the paramount goal of protecting public health.

References

1. Cesari M, Prince M, Thiyagarajan JA, et al. Frailty: An emerging public health priority. J Am Med Dir Assoc. 17(3):188-192 (2016).
2. Nanna MG, Wang SY, Damluji AA, et al. Management of stable angina in the older adult population. Circ Cardiovasc Interv. 16(4):e012438 (2023).
3. Tan Z, Shang X, Li L, et al. Clinical study of isosorbide mononitrate treatment for angina pectoris in coronary heart disease. Exp Ther Med. 5(4):1133-116 (2013).
4. Schwartz BG, Kloner RA. Drug interactions with phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. Circulation. 122(1):88-95 (2010).
5. ISORDIL® titradoseTM (Isosorbide Dinitrate) tablets rx only description. (2014).
6. MHRA. Information for the patient isosorbide dinitrate tablets. (2022).
7. Fung HL. Pharmacokinetics and pharmacodynamics of isosorbide dinitrate. Am Heart J. 110(1):213-216 (1985).
8. Spörl-Radun S, Betzien G, Kaufmann B, et al. Effects and pharmacokinetics of isosorbide dinitrate in normal man. Eur J Clin Pharmacol. 18(3):237-244 (1980).
9. Boolell M, Gepi-Attee S, Gingell J, et al. Sildenafil, a novel effective oral therapy for male erectile dysfunction. Br J Urol. 78(2):257-261 (1996).
10. Momtaz MA, El-Desoky HS, Rehab A, et al. Quality-by-design optimized HPLC approach for the therapeutic drug monitoring of isosorbide dinitrate and sildenafil in human plasma samples. Talanta Open. 2025:100540.
11. Kang J-S, Lee M-H. Overview of therapeutic drug monitoring. Korean J Intern Med. 24(1):1 (2009).
12. Beach ES, Cui Z, Anastas PT. Green chemistry: A design framework for sustainability. Energy Environ Sci. 2(10):1038-1049 (2009).
13. Holm P, Allesø M, Bryder MC, et al. Q8 (R2) pharmaceutical development. ICH quality guidelines: An implementation guide. 2017:535-77.
14. Nichols DJ, Muirhead GJ, Harness JA, et al. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: Absolute bioavailability, food effects and dose proportionality. Br J Clin Pharmacol. 53:5S-12S (2002).
15. Kang JS, Lee MH. Overview of therapeutic drug monitoring. Korean J Intern Med. 24(1):1 (2009).
16. Kloner RA. Cardiovascular risk and sildenafil. Am J Cardiol. 86(2):57-61 (2000).
17. Jackson G, Montorsi P, Cheitlin MD, et al. Cardiovascular safety of sildenafil citrate (Viagra®): An updated perspective. Urology. 68(3):47-60 (2006).
18. Beach ES, Cui Z, Anastas PT, et al. Green chemistry: A design framework for sustainability. Energy & Environ Sci. 2(10):1038-1049 (2009).
19. Holm P, Allesø M, Bryder MC, et al. Q8 (R2) Pharmaceutical development. ICH quality guidelines: An implementation guide. 2017:535-577.
20. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. Br J Clin Pharmacol. 53:5S-12S (2002).